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Mini-review

Connecting cancer relapse with senescence

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ABSTRACT

Many cancers respond to initial treatment but most of them relapse due to the persistence of dormant tumor cells. Determining the exact nature of the dormant state is crucial to develop therapies aiming to eradicate the dormant cells. Here, we argue that therapy-induced senescence of cancer cells could be an alternative form of dormancy.

1. Introduction

Although most patients with cancer can be cured, some of them relapse years or decades after the initial treatment or even during maintenance therapy. The biological mechanisms that allow cancer recurrence remain poorly understood, especially in the case of late recurrence (relapse after a full remission in the absence of maintenance therapy). This late reactivation can only be explained by the persistence of dormant residual cancer cells. Since relapse is the main cause of cancer-related death, the cellular and molecular characterization of the dormant state is essential for its eradication.

These residual dormant cancer cells are assumed to be pre-existing cancer cell subtypes whose core characteristic is plasticity, enabling them to resist anti-cancer treatment, to remain alive in the body over the long term, and then to regenerate a diversity of new cancer cells with equal or even more aggressive characteristics. This plasticity is shared by several subtypes of cancer cells, notably cancer stem cells (CSCs) also referred to as tumor-initiating cells (TICs), circulating tumor cells (CTCs), disseminated tumor cells (DTCs), and metastasis-initiating cells (MICs). A growing body of evidence indicates that these cancer cell subtypes could all provide the cohort of dormant cells and be at the origin of relapse [1,2]. The molecular dormancy signature includes regulators of quiescence [3], which could explain why dormant cells are protected from the standard anti-cancer genotoxic treatments designed to target proliferating cells. Dormant cells are also often insulated from cell death signals inside a protective microenvironment [4]. When conditions change, dormant cells could restart proliferation as a consequence of genetic or epigenetic alterations or in response to non-cell autonomous signals [5]. Some studies also suggest that residual dormant cancer cells could be common cancer cells reprogrammed to dormancy by the anti-cancer treatment, i.e. reprogrammed to a cancer stem-like state [6].

Clinical data show that many anti-cancer agents have the ability to induce senescent(-like) phenotypes in a subset of treated tumor cells [7]. Senescence is considered to be a tumor suppressor mechanism which halts proliferation of cells at risk, such as normal cells having activated an oncogene, as well as malignant cells having received an anticancer treatment. However, emerging evidence indicates that rare senescent cells can escape from senescence programs to re-enter the cell cycle and promote tumor progression [8]. Therefore, senescent cancer cells, like dormant cells, reprogram following the anti-cancer treatment to adapt and resist it, survive long term, and then eventually escape to regenerate new cancer cells. We will review here the evidence for post-senescence neoplastic escape from senescence programs, in particular therapy-induced senescence (TIS). We will also highlight the properties and pathways of cancer cells escaping from senescence programs including TIS, and suggest that TIS may be a mechanism that sustains the minimal residual disease, as an alternative or a companion to the dormancy of CSCs.

2. The senescent phenotypes

Senescence is a complex cellular state which needs to be defined according to several criteria. Senescent cells are long-lived, metabolically active and characterized by a specific set of phenotypic and molecular alterations [9], leading to profound changes in their transcriptome, proteome and secretome [10–13]. As stressed cells, senescent cells

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display an enlarged morphology, changes in the organization of chromatin with the appearance of senescence-associated heterochromatin foci (SAHFs) [14–16], as well as polynucleation [17,18]. Senescent cells are also characterized by dysfunctional mitochondria [15], endoplasmic reticulum stress [19], high autophagic activity [20], endogenous oxidative stress [21] and unrepaired DNA damage [22]. Senescent cells are resistant to apoptosis compared to normal growing cells [23,24]. They develop a modified secretome, the senescence-associated secretory phenotype (SASP), characterized by high levels of pro-inflammatory cytokines, growth factors, remodeling enzymes of the extracellular matrix and changes in extracellular matrix structural components [13]. Senescence-Associated-β-Galactosidase (SA-β-Gal) activity is a commonly used senescence marker [25], although its mechanistic contribution remains unclear [26]. The major hallmark of senescence is the robust cell-cycle arrest, mainly controlled by the p53/p21^{WAF1} and p16^{INK4A}/Rb pathways. These pathways are activated by the presence of unrepaired DNA damage induced by various endogenous or exogenous stresses, as well as damage to other cell components [27]. Several of these phenotypic traits are used as senescence markers *in vitro* and/or *in vivo*. Interestingly, regarding the potential role of senescence in tumor dormancy, the most recent studies have linked senescence to a stem cell phenotype [28–33].

3. Cancer cells can undergo therapy-induced senescence

Senescence is a reprogrammed state that can be induced by various stimuli. Different subtypes of senescence have been defined, depending on the causal stressor. The main interest of this classification is to position senescence in its physiological, pathological or clinical context, without any major underlying differences in phenotypes or specific mechanisms. However, some senescent characteristics may differ depending on context and cell type. For instance, SAHFs and heterochromatin compaction seem to vary depending on the experimental model [34]. Regarding the main effector pathways – DNA damage, oxidative stress, p53/p21^{WAF1}, p16^{INK4A}/Rb - it is likely that their degree and kinetics of activation may differ depending on the exposure, acute or chronic, to the senescence inducer.

Replicative senescence (RS) was the first senescence subtype to be described [35]. The stressor is successive replication cycles leading to telomere shortening and deprotection. The deprotected telomeres are sensed as unrepaired double-strand breaks, resulting in the persistent activation of the DNA Damage Response (DDR) pathway and consequently in an irreversible cell-cycle arrest through activation of the p53/p21^{WAF1} pathway [15]. Telomere shortening is accompanied by an increase in oxidative stress that induces DNA damage and damage to other cell components, notably mitochondria, leading to an additional activation of the p16^{INK4A}/Rb pathway [36].

The second senescence subtype is stress-induced premature senescence (SIPS). SIPS is a senescent state induced a few days following a stress, usually oxidative stress. SIPS results mainly from accumulation of oxidative damage, including DNA damage and damage to other cell components [37–40]. It is by essence independent of telomere shortening, although telomeric sequences could be more sensitive to oxidative damage [41] and are almost irreparable [42]. Depending on the nature and quantity of the damage, the cell cycle arrest associated with SIPS is mediated through activation of the DDR and p53/p21^{WAF1} pathways, through activation of the p16^{INK4A}/Rb pathway, or through both [36,37,43].

The third senescence subtype is oncogene-induced senescence (OIS), which is observed upon hyper-activation of oncogenes such as BRaf, Ras or Rel/NF-κB [44–46]. OIS is independent of telomere shortening [47] and operates through the generation of oxidative and replicative stresses, leading to the activation of the p53/p21^{WAF1} and p16^{INK4A}/Rb pathways [43].

The last senescence subtype was proposed more recently. It is therapy-induced senescence (TIS) induced by the genotoxic agents used in anti-cancer therapies, including ionizing radiation used in radiotherapy, DNA damaging chemicals (for example adriamycin, cisplatin) used in several chemotherapies and even microtubule poisons that do not directly generate DNA damage but cause oxidative stress (Fig. 1). TIS is not fundamentally different from SIPS, although the term is generally used when the affected cells are cancer cells. Although cancer cells were long assumed to be incapable of undergoing senescence, numerous data now demonstrate that various types of tumor cells do undergo TIS in response to many anti-cancer agents [7,48–61]. The cell cycle arrest in TIS is mediated by the p53/p21^{WAF1} and/or p16^{INK4A}/Rb pathways, as in SIPS, provided that these pathways are still functional in the cancer cells. However, some studies have observed an induction of TIS even in cancer cell lines with non-functional p53, through several compensatory pathways [7]. The existence of TISis supported by *in vivo* data, for instance by the identification of large SA-β-Gal-positive areas in lung tumor patients treated with carboplatin and docetaxel compared to untreated patients [62], or in breast tumors after cyclophosphamide, doxorubicin, and 5-fluorouracil treatment [50]. Also, biopsies from human prostate cancer patients treated with mitoxantrone showed higher levels of p16^{INK4a} and p21^{WAF1} mRNAs compared to biopsies before treatment [13]. Senescence markers including PAI1 and p21^{WAF1} were shown to be upregulated in tumors of patients with malignant pleural mesothelioma after neo-adjuvant platinum-based chemotherapy. This was associated with a poor response to treatment [63]. In addition, a recent paper showed that different types of chemotherapy with unrelated mechanisms of action (including doxorubicin, paclitaxel, temozolomide, cisplatin) injected in a mouse model in which p16^{INK4A}-positive senescent cells can be detected, led to senescence of different cell types in different tissues [64].

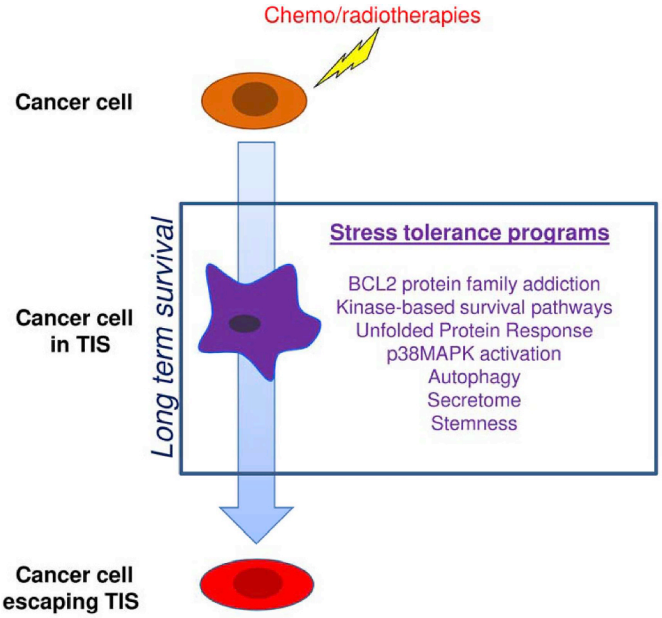

Fig. 1. Senescence as a mechanism of cancer cell survival and cancer relapse. Many anti-cancer agents induce a premature senescent state known as therapy-induced senescence (TIS). Cancer cells in TIS are cell cycle arrested but survive long term. Their long-term survival requires the activation of several stress tolerance programs. Some rare cancer cells in TIS can recover the ability to re-enter the cell cycle to generate cancer daughter cells that are more transformed than the original cancer cells. This may be one mechanism by which cancer relapse occurs.

4. Long-term survival and stress tolerance of cancer cells in TIS: a property compatible with a role in the minimal residual disease

Senescent cells are resistant to apoptotic cell death, and this is certainly one major mechanism responsible for their long-term survival. In fact, cancer cells in TIS and cancer stem cells share several survival

pathways, supporting the idea that TIS could be an alternative form of dormancy.

Apoptosis evasion is one of the most common hallmarks of cancer progression and the balance between pro-apoptotic and anti-apoptotic factors is tipped towards BCL-2 survival members in most cancers. Several studies have described the addiction of senescent cells, including cancer cells in TIS, to BCL-2, BCL-xL or MCL1 [52,65,66], indicating that these cells express active death signals that need to be constantly inactivated. BCL-xL was shown to play a critical role in breast cancer dormancy and to regulate the metastatic potential of dormant cells [67].

Another survival pathway shared by cancer cells in TIS and dormant cancer cells is the Ephrin pathway. Ephrin receptors are expressed by senescent cells and targeting their expression induces cell death [68]. Interestingly, the Eph receptor A5 has been characterized as a dormancy-specific biomarker [69]. EphA5 mRNA expression was found to be upregulated in dormant glioblastoma and dormant liposarcoma cell lines. Moreover, increased EphA5 plasma levels were reported in mice bearing dormant glioblastoma compared with control mice [69].

We have shown that the NF-κB > MnSOD > H_2O_2 pathway is involved in the occurrence of senescence in normal human epidermal keratinocytes (NHEKs) [46]. This axis is also responsible for the induction of an autophagic activity by causing oxidative damage to the mitochondria and nucleus [70]. The survival of the senescent NHEKs depends at least in part on the level of autophagic activity, which has to be high enough to eliminate the toxic oxidized cell components but not so high as to cause autophagic cell death [71]. Regarding TIS, Goehe et al. showed that autophagy accelerates the onset of senescence induced by doxorubicin or camptothecin in MCF7 or HCT116 cancer cells, through a reactive oxygen species- and p53-dependent pathway [72]. A recent report demonstrated the crucial involvement of autophagy in senescence of U2OS and RPE-1 cells treated with the antimitotic drug nocodazole, through the activation of the AMPK/ULK/mTOR axis [73]. Thus, increased levels of autophagy contribute to the survival of senescent cells [20,43,70,71]. Similarly, a recent report showed that breast dormant tumor cells are autophagic and inhibition of autophagy *in vivo* impaired their survival. The authors also showed that activated autophagy is a process maintained in breast dormant cells, but reduced once the exit of dormancy occurs [74].

Different types of endogenous or exogenous stresses induce an endoplasmic reticulum stress, to which cells can adapt through activation of the unfolded protein response (UPR) [75]. Both senescent (RS and TIS) and dormant cells activate this pathway and its inhibition affects their survival. For instance, the UPR marker PDI is increased in both senescent [76] and dormant cells from patients [77]. When ATF6α, one arm of the UPR, is downregulated, it abolishes the long-term survival of dormant cells and their resistance to chemotherapy [78,79]. It also leads to a partial reversion of the replicative senescent phenotype and decreases specific SASP cytokines [76]. Stress adaptation in dormant and senescent cells is also regulated by kinases such as mTOR and p38MAPK [80]. The latter promotes the survival of dormant cells through ATF6α/Rheb/mTOR signaling [78] and also plays a role in the induction and maintenance of senescence [22,81,82].

5. Escape from senescence: a mechanism possibly at the origin of cancer relapse

Based on historical studies performed on RS, cellular senescence was defined as an irreversible cell cycle arrest, and for that reason, it was seen as an anti-tumor barrier [83]. According to this paradigm, the early evidence that cancer cells can enter senescence positioned TIS as a new anti-cancer therapy, which does not enable eradication of the tumor, but does stop its growth. The main advantage of this potential new anti-cancer therapy is that TIS can generally be induced at doses of radio/chemotherapies lower than those inducing cancer cell death, thus offering hope of reduced adverse effects [7].

However, a growing number of recent studies, including from our groups, have described events of senescence escape by both normal cells in SIPS or OIS, or cancer cells in TIS, but never by cells in RS. The resulting daughter cells often display transformed properties more pronounced than that of their parental cells.

5.1. Evidence of post-senescence neoplastic escape following SIPS and OIS

The first evidence of post-senescence neoplastic escape was obtained, including by our group, with normal epithelial cells, namely Human Mammary Epithelial Cells (HMECs) and Normal Human Epidermal Keratinocytes (NHEKs). *In vitro*, these cells spontaneously enter in SIPS after a few population doublings and then, systematically, some rare senescent cells re-renter the cell cycle to generate daughter cells with tumorigenic potential [84–87]. The post-senescent cells are distinct from the parental population with features including epithelium-to-mesenchyme transition (EMT), genetic instability and aggressiveness. Their EMT is characterized by an epithelioid to fibroblastoid shift in morphology. They grow faster in a culture medium designed for fibroblasts than in their parental culture medium designed for NHEKs. At the molecular level, they display reduced levels of E-cadherin and increased levels of vimentin. They express the EMT specific Twist1 proteins [86]. NHEKs that escaped from SIPS do not display gross chromosomal aberrations [85], but have acquired discreet mutations which were absent in their normal parental cells [22]. Subcutaneous injection of NHEKs that escaped SIPS in *nude* mice resulted in disseminated skin lesions characterized as hyperplasias and small non-melanoma skin carcinomas. This strongly suggests that these post-senescent cells have acquired a tumorigenic potential, although they were originally derived from normal cells. Transcriptomic analyses support this notion since the molecular signature of emergent cells comprises a high proportion of genes deregulated in psoriasis and premalignant skin lesions including actinic keratosis and arsenic-induced cutaneous hyperplastic lesions [85,87]. Importantly, using different approaches (limit dilutions, cell sorting experiments and videomicroscopy), we demonstrated that the post-senescent emergent cells were generated from cells displaying a marked senescent phenotype [22,71,85].

Escape from OIS has been demonstrated in several cell types. Melanocytes induced in senescence by N-Ras61K give rise after long term culture to post-senescent cells with several chromosomal aberrations, an ability to grow in soft agar, and expressing stem-like and meiosis-associated genes [88]. We demonstrated that malignant HT29 colon cancer cells can escape from RAS-induced senescence. The emergent cells have enhanced migration and invasion capacities, a reduced expression of E-cadherin and an increased expression of dedifferentiation markers. They display more DNA damage than their parental cancer cells [55], probably resulting from replicative stress. Similarly, the Gorgoulis group demonstrated that a subset of cells from a bone osteosarcoma SAOS2 cell population in which a doxycycline-inducible $p21^{WAF1/Cip1}$ expression has been introduced, are able to escape p21-mediated senescence to re-enter the cell cycle and generate daughter cells with more invasive characteristics [89].

5.2. Evidence of post-senescence escape following TIS

Importantly, escape from TIS has been demonstrated for a variety of cancer cell types [52,90,92,95,96]. One of the best examples was provided by the study of Saleh et al. [90]. They demonstrated with three cancer cell lines (H460 non-small cell lung cancer cell line, HCT116 colorectal carcinoma cell line and 4T1 breast cancer cell line) with different p53 status that subpopulations of senescent cells sorted on their high expression of senescence markers were able to escape TIS induced by topoisomerase II poisons (etoposide and doxorubicin) and resume proliferation. This ability to escape was present even after a forced arrest in senescence for 25 days. The escape from TIS was demonstrated *in vitro*, but also *in vivo*: SA-β-Gal-positive 4T1 cells

implanted into the mammary fat pad of mice developed tumors after 19–25 days.

One hallmark of cells having escaped from TIS is that they were shown in some experiments to be more transformed than their parental cancer cells, more aggressive, and more resistant to anti-cancer therapies. Using colorectal or breast cancer cells, we initially demonstrated that cells preferentially entered TIS in response to topoisomerase I inhibitor (irinotecan) treatment and emergent cells that resume proliferation appeared after 10 days. Importantly, this emergent population displayed the same sensitivity to the initial treatment as parental cells, indicating that escape from TIS was not related to selection of a resistant clone. Emergent cells divided less efficiently than the parental ones, but were more able to grow in soft agar. However, they were no more efficient than parental cells to form tumors [52]. In contrast, other authors were able to isolate a clone of mammary cells having escaped from TIS induced by adriamycin which acquired cross-resistance to other chemotherapeutic agents such as camptothecin and teniposide and also to γ-irradiation [92]. A study based on comparative genomic hybridization performed on cells which escaped cisplatin-induced senescence in PROb colon tumor in a rat model found chromosomal aberrations (deletions and amplifications) on chromosomes 4, 9, 11, 12, 15, 19 and X which were not present in the parental PROb cells. These mutated emergent cells had an increased resistance to cytotoxic drugs and reconstituted tumors that grew like the PROb parental tumors [95]. Cells that escaped TIS have also been shown to have a higher potential to initiate tumorigenesis, as described in a genetically switchable model of B-cell lymphoma which entered TIS upon adriamycin treatment and in which the senescence escape was genetically induced by switching off p53 or Suv39h1 [96]. It is clear from all these studies that cells that escape TIS are at least as neoplastic as their parental cancer cells, if not more so. However, further studies are required to better characterize the tumor initiation potential of TIS-escaped cells, as well as their metastatic potential, the two most important parameters in cancer disease relapse.

5.3. Mechanisms underlying escape from senescence programs

5.3.1. Epigenetic alterations and expression of cell cycle/survival regulators

In order to produce a progeny of post-senescent neoplastic cells, at least a few senescent cells have to re-enter the cell cycle. Therefore, the question arose of whether this subpopulation of senescent cells could have downregulated the p53/$p21^{WAF1}$ and/or $p16^{INK4A}$/Rb pathways.

The first studies addressing this question were performed on HMECs in SIPS. They highlighted a downregulation of p16 through methylation of its promoter [97–99]. Further studies revealed hundreds of aberrant hyper- and hypomethylation events, suggesting that large-scale epigenetic remodeling is necessary for senescence escape [100]. Recent results have shown that the LSD1 and JMJD2C demethylases induce senescence escape of melanoma cells in TIS to favor cell transformation [101]. In addition, we have shown that upregulation of the EZH2 methylase is necessary for TIS escape [102].

In most *in vitro* cancer cell lines, $p16^{INK4A}$ is inactivated. We have shown that, in this condition, TIS induction relies on $p21^{WAF1}$ activation. Paradoxically, our results indicate that in addition to their role in TIS induction, p53 and $p21^{WAF1}$ are also indispensable for TIS escape [103].

H1299 or MCF7 tumor cells that escape from TIS overexpress the cyclin-dependent kinase CDK1, whereas CDK1 activity is downregulated in the average senescent population [62,92,104]. Similarly, high phospho-CDK1 levels were found in glioblastoma cells escaping from senescence induced by irradiation [91]. CDK1 appears necessary for escape from TIS, since inhibition of CDK1 prevents it [62]. It is likely that CDK1 activity is partially controlled by p27 rather than by $p21^{WAF1}$ [104].

A role for the Akt pathway in senescence escape was initially proposed in the context of OIS. For instance, Akt activation following PTEN downregulation by shRNA induced escape from Raf-mediated senescence in melanoma cells [105]. In colorectal cancer cells, Akt downregulation prevents TIS induction by irinotecan and induces cell death as a consequence of Noxa upregulation. This completely prevents the emergence of more transformed cells [103]. In colorectal cancer cells, we have shown that the inhibition of some anti-apoptotic members of the BCL-2 family, Mcl-1 and Bcl-xL, completely prevents the escape from OIS or TIS of aggressive cells [55,103]. Therefore, the inhibition of cell death pathways during TIS appears to be a prerequisite for escape to occur.

Our group recently identified thrombospondin 1 (TSP1) as a protein secreted by senescent cells to maintain the proliferative arrest. We observed that cells that escaped TIS have reduced expression of the TSP1 receptor, the CD47 protein. In addition, $CD47^{low}$ emergent cells also have a reduced expression of $p21^{WAF1}$, which is essential for maintenance of the proliferative arrest. We thus identified the $CD47^{low}$ senescent cells as the subpopulation able to escape TIS [106].

5.3.2. Oxidative DNA damage

We have shown that the accumulation of reactive oxygen species (ROS) in NHEKs during SIPS through activation of the NF-κB/MnSOD axis coupled to an absence of H_2O_2-degrading enzymes results in senescence evasion also called “post-senescence neoplastic emergence” (PSNE). Inhibition of NF-κB activity or cell treatment by antioxidants strongly reduced the frequency of PSNE [85]. We have also demonstrated that oxidative stress and the subsequent generation of DNA single-strand breaks (SSBs), as well as downregulation of PARP1, the enzyme that recognizes SSBs and initiates their repair, are necessary and sufficient for causing PSNE, suggesting that the mutagenicity of accumulated unrepaired SSBs is what drives the process [22]. A premature senescence plateau followed by PSNE was observed when exponentially growing NHEKs were treated with ROS. In contrast, the presence of antioxidants delayed the occurrence of senescence and inhibited PSNE [85]. Therefore, the oxidative stress, and the DNA damage it induces, are involved in both the establishment of SIPS and the escape from SIPS. Whether such a mechanism would be involved in the escape from TIS is plausible, because most chemotherapies and radiotherapies produce oxidative stress, but this has to be documented. One study reported that HCT116 cells induced in TIS by doxorubicin treatment suffered from oxidative stress resulting from an increase in defective mitochondria. An antioxidant treatment by Trolox prevented the cells from escaping TIS [93].

5.3.3. Polyploidy and acquisition of stemness

Interestingly, the multinucleation/polyploidy of senescent cells, a long-established but still puzzling phenotypic trait of senescence, may represent an important transition state by which escape from senescence could preferentially occur. First, microscopic examinations and video-microscopies showed that emergent cells mainly come from enlarged multinucleated/polyploid senescent cells [85,88,95,104,107,108] through an unusual asymmetric mitosis mechanism (called budding or neosis) in epithelial cells undergoing SIPS [85,107]. N-Ras61K-induced senescence is also associated with an accumulation of multinucleated cells. These multinucleated cells triggered the emergence of tumor cells escaping OIS. Expression profiling of these emergent cells revealed that meiosis genes including Spo11 were markedly increased [88]. Interestingly, the upregulation of Spo11 was independently associated with depolyploidization [109]. In the context of TIS, a study reported that cisplatin exposure in PROb cells induced polyploidization through endoreplication in parallel to the establishment of a senescent-like phenotype. The long-term culture of these multinucleated senescent cells led to the generation of cells escaping cisplatin-induced senescence [95]. Another study showed that doxorubicin-induced senescence in HCT116 cells led in parallel to intensive polyploidization and ROS production [93]. The same study demonstrated that modulation of the expression of mTOR and/or Pim-1 kinases may control ploidy upon cell

senescence [93]. Indeed, mTOR was associated with the development of cell polyploidization [110] and its inhibition prevented the induction of polyploidy/senescence in breast cancer cells [111]. Another study showed that the accumulation of polyploid senescent cancer cells was associated with reduced expression of Cdk1, and the small proportion of polyploid senescent cells that still expressed high levels of Cdk1 were identified as the progenitors of the escaped cells [104].

Recently, Milanovic et al. showed that senescence escape is associated with a gain of stemness and a higher tumor-initiating potential [96]. This idea is also supported by studies indicating that stemness markers including Pdpn, Nanog, CD133, CD34, and CD117 are upregulated in cells escaping from TIS and also from OIS [88,91,94]. Interestingly, increased levels of NANOG were shown to be associated with depolyploidization [112]. Therefore, although all these studies strongly support a role for multinucleation/polyploidy in the process of post-senescence emergence, further research will be needed to understand how multinucleation/polyploidy proceeds to allow mitosis of cells as large as senescent cells, and whether it plays a role in the transmission of transformed and stemness characteristics to the daughter cells.

6. Senescent cells create a microenvironment favoring dormancy and relapse

One of the widely studied phenotypes associated with senescence is the change in the composition of the secretome, called the SASP. Although the SASP can reinforce senescence and stimulate immune surveillance against senescent cells [113], SASP components can also have a pro-tumoral effect [114,115]. This effect was demonstrated for example in breast cancer cells and in xenografted tumors [116]. Importantly, SASP components are unable to stimulate the proliferation of normal epithelial cells, indicating that the pro-tumoral effect only concerns already transformed cells. Anti-cancer therapies target cancer cells but also inevitably affect stromal populations, which could therefore also undergo TIS. As a result, if not timely cleared, both cancer and stromal cells entering TIS will produce a SASP that could contribute to modify the tumor microenvironment to make it more pro-tumoral. This was elegantly demonstrated using the p16-3MR mouse model. These mice express functional domains of the luciferase and red fluorescent proteins under the control of the $p16^{INK4a}$ promoter. Upregulation of $p16^{INK4a}$ and senescence induction were detected by imaging in several tissues following treatment with various genotoxic drugs. The presence of these normal cells in TIS created a deleterious, inflammatorymicroenvironment leading for instance to cardiac abnormalities, and to increased tumor progression and metastatic spread. Importantly, the elimination of senescent cells reduced cancer relapse and dissemination [64]. The pro-tumoral effect of the SASP is mediated by an increase in synthesis and secretion of inflammatory cytokines, growth factors and pro-angiogenic factors [114]. For example, TGFβ, which is over-secreted by senescent cells, contributes to enhance RAS-induced senescence [117] but also to reactivate metastatic growth of dormant DTCs [118].

In addition to its pro-tumoral effet, the SASP could also have a pro-tumorigenic effect by favoring senescence escape. Matrix metalloproteases have been shown to participate in this pro-tumorigenic effect by senescence escape. Our group showed that MMP1 and 2, which are components of the SASP of fibroblasts in RS, increase the frequency of senescence escape of NHEKs in SIPS, favor an epithelium-to-mesenchyme transition in the escaped cells and enhance their metastatic spread [28,86]. However, to our knowledge it has never been determined whether this pro-tumorigenic effect by enhancement of escape from senescence also applies to cancer cells in TIS.

Overall, these studies indicate that stromal and cancer cells in TIS could modify their own microenvironment in several ways that: i) favor the maintenance and even the propagation of senescence, ii) favor senescence escape, iii) enhance the proliferation and dissemination of escaped cells once generated and iv) enhance the proliferation and dissemination of bona-fide cancer cells. These properties of the SASP could therefore positively contribute to tumor dormancy and cancer relapse.

7. Targeting cancer cells in TIS to prevent cancer relapse

If senescence is an alternative or a companion form of tumor dormancy as argued above, targeting cancer cells in TIS with senolytics might be a way to prevent cancer relapse. Senolytics are pharmacological drugs able to specifically or preferentially kill senescent cells by targeting their survival pathways. The two main currently characterized senolytics in mouse models are BH3 mimetics, such as ABT-263 (Navitoclax) and ABT-737 which inhibit anti-apoptotic proteins of the BCL-2 family (BCL-2, BCL-X, BCL-W and MCL-1), and the association of dasatinib and quercetin which targets a large spectrum of kinases as well as dependence receptors of the Ephrin pathway [66,119]. Senolytics could be used as adjuvant therapy to eradicate the cancer cells that resisted the initial treatment by undergoing TIS rather than cell death (Fig. 2). The benefit could be triple: i) eliminate the cancer cells in TIS prone to neoplastic escape. In support of this, Demaria et al. showed that eliminating cancer cells in TIS with senolytics reduced cancer relapse in mice treated with doxorubicin [64]; ii) suppress the SASP and its oncogenic effects and iii) reduce the dose of the initial anti-cancer treatment and hence its adverse effects, since lowering the chemo/radiotherapy doses favors senescence induction rather than apoptosis.

One challenge in using senolytics is that senescence is a complex, possibly heterogeneous, phenotype. The activated cell cycle arrest and survival pathways might differ according to the cell type and/or the applied anti-cancer therapy, or might be activated to different degrees, leading to a more or less deep senescent phenotype, more or less stable, more or less prone to escape. Similarly, it is tempting to speculate that the composition of the SASP of cells in TIS could vary subtly from one patient to another, generating a niche more or less favoring dormancy maintenance versus dormancy exit. For these reasons, senolytic treatments would have to be tailored to each patient.

Personalization of senolytic treatments, would first have to involve a search for markers able to distinguish cancer cells that have entered a stable senescence program, which could sustain a long-term curative effect, from those prone to escape the suppressive arrest which could lead to cancer relapse. Checking the activation of the DDR pathway could be of interest, because its strong activation is one mechanism underlying the irreversibility of the senescent cell cycle arrest [53]. In contrast, the sole activation of the SSBR (single-strand break repair) pathway could indicate a risk of post-senescent escape, as we have shown for NHEKs undergoing SIPS [22]. BH3 profiling could be used to identify cancer cells in TIS that are especially addicted to BCL-2 survival proteins and therefore especially sensitive to BH3 mimetics. Moreover, as different senolytics have different affinities for BCL-2 family proteins, BH3 profiling could help to identify which BCL-2 family protein is specifically expressed in order to choose the most suitable BH3 mimetic. Considering the clonal heterogeneity of tumors, combinations or sequential application of different types of senolytics should therefore be tested. The recently described senescence markers DPP4 and SCAMP4 could also be of potential interest to identify different subpopulations of senescent cells with different oncogenic properties [120,121].

Another challenge in using senolytics is to determine when to introduce the senolytic relative to the first-line anti-cancer therapy. Since senescence is a rather stable phenotype and since senescent cells do not proliferate, a first possibility would be to allow a grace period after the end of the chemo/radiotherapy before introducing the senolytic. The advantage for the patient would be a quiet-time between two treatments. The risk would be that during that time interval, escape from TIS would have already begun. Therefore, it would be very important to

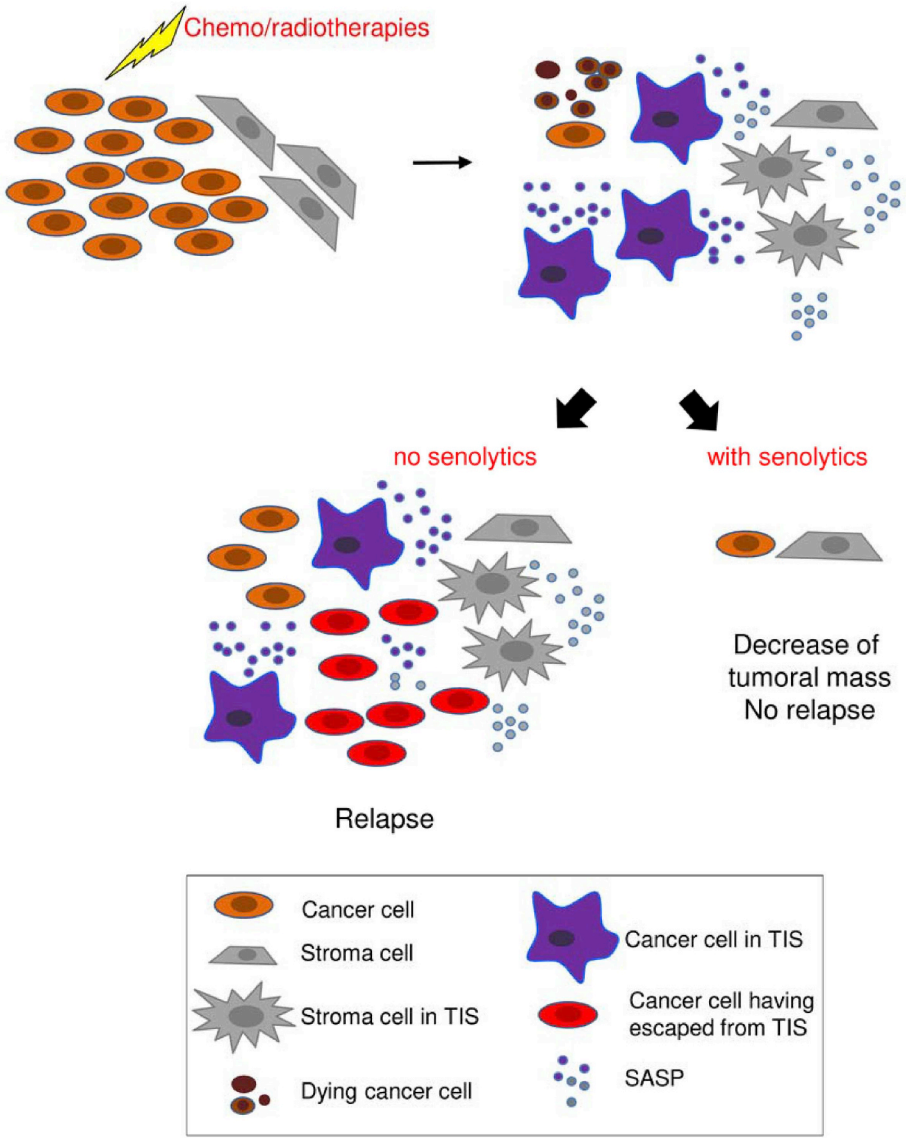

Fig. 2. Senolytics to eliminate cancer and stromal cells in TIS and prevent cancer relapse. Chemo/radiotherapy treatments primarily cause the death of cancer cells, while inducing premature senescence in a subset of cancer and stromal cells, thus procuring an immediate curative effect. However, as time goes by, cancer and stromal cells in TIS could favor cancer relapse through cell autonomous and non-cell autonomous mechanisms. The cell autonomous mechanism is the ability of some rare cancer cells in TIS to re-enter the cell cycle to generate cancer daughter cells with more aggressive characteristics. Non-cell autonomous mechanisms are mediated by the inflammatory and pro-tumorigenic properties of the SASP of cancer and stromal cells in TIS, which can promote the proliferation of the post-senescent escaped cancer cells as well as the original cancer cells that may have resisted the treatment. Senolytic treatments, combined with first-line therapies or applied as a maintenance therapy, may target and kill some or all TIS subpopulations. This should further decrease the tumor mass, suppress the SASP, and thereby contribute to reduce the risk of cancer relapse.

determine whether senolytics could also send the post-TIS cells to death. Another possibility is to introduce the senolytic in combination with chemo/radiotherapy, but in that case the markers described above could not be used.

8. Conclusions

All the data presented in this review clearly indicate that senescence occurring in normal cells or in cancer cells can no longer be defined as a definitive anti-proliferative state but more as a stress-response adaptive state, from which, depending on the cell type and on the nature, strength and duration of the stress, some rare cells can re-enter the cell cycle to generate daughter cells that have acquired new neoplastic properties. There are striking parallels between the senescent state as characterized in cancer cells after anti-cancer therapy and the dormancy state of cancer cells as represented by CSCs, CTCs or DTCs. If true, this means that cancer cells entering TIS could be considered as components of the minimal residual disease and be at the origin of tumor relapse. This should incite further studies on the pathways specifically involved in senescence induction, senescence maintenance and senescence escape in order to identify new avenues for the treatment of the cancer minimal residual disease. Senolytics seem very promising in this regard. However, they themselves could have undesirable effects on normal tissues, although the available studies in mouse models have not so far highlighted such difficulties.

Conflicts of interest

The authors declare that they have no competing interests.

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